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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,116	05/19/1999	DOUGLAS ANTELMAN	16930-0010-2	6044

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EXAMINER
CHEN, LIPING

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 07/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

corrected to show 892 form

Office Action Summary	Application No.	Applicant(s)	
	09/315,116	ANTELMAN ET AL.	
	Examiner	Art Unit	
	Liping Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-37* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-30 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

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6) ☐ Other:

DETAILED ACTION

Status of the claims

A restriction was made on 07/05/2001. Applicant's election of group II, claims 16, 17-30 and 37, drawn to a method for treating a hyperproliferative disorder, comprising administering a nucleic acid encoding a fusion protein comprising a DNA biding domain of a transcriptional factor and a functional growth suppression domain of a retinoblastoma (RB) polypeptide with traverse to the species election and splits a single claim, i.e. claim 16, in Paper No. 12 is acknowledged. Applicant argues that "the courts have long held that the section of the patent statute that authorizes restriction practice, i.e., 35 U.S.C. §121, provides no legal authority to imposes a restriction on a single claim, even if the claim presents multiple independently patentable invention". However, under 35 U.S.C 121, it is clearly states "If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions." It is clear that claim 16 containing multiple inventions according to the definition of hyperproliferative disorder by applicant (specification, page 15, line 15 to page 16, line 2). Claim 16 encompasses distinct inentions and is not a proper generic claim because claim 17 does not properly limit claim 16 (see rejection below under 35 U.S.C. 112, 2nd paragraph).

Claims 16-37 are pending and claims 16-30 and 37 will be examined in this office action on the merits according to Group II.

Priority

This is a U.S. application filed on 05/19/1999,
which is a DIV of 08/801,092 filed on 02/14/1997, PAT 6,074,850,
which is a CIP of 08/751,517 filed on 11/15/1996, ABD

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-30 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a method for treatment of a hyperproliferative disorder in a patient comprising administering to a patient a therapeutically effective dose of a nucleic acid encoding a fusion polypeptide or a fusion polypeptide that comprises a DNA binding domain of a transcription factor, or E2F, or amino acid residues 95-286 or 95-194 of E2F, and a functional growth suppression domain of a retinoblastoma (RB) polypeptide, or amino acid residues of 379-928 of RB, or a RB polypeptide comprises at least one substitution of amino acid residues selected from the group consisting of 2, 608, 612, 788, 807, and 811. The

specification only provides a list of hyperproliferative diseases including non-pathologic and pathologic hyperproliferative diseases, such as restenosis, diabetic retinopathy, thyroid hyperplasia and different cancers such as breast cancer, sarcomas, lung cancer, various leukemias, lymphomas and bladder cancer (specification, page 15, line 15 to page 16, line 2). Cancer, as the most challenge hyperproliferative disease, has been known for long time as a result of the accumulation of multiple abnormalities and a result of complex multistep process (Cooper, Oncogenes, Jones and Bartlett Publishers, 1990, page 4, last parag.) and many tumor oncogenes (Cooper, page 76, Table 5.1, page 89, Table 6.1 and page 112, table 8.1) and tumor suppressor genes (Cooper, page 132-135) have been recognized to be related with certain type of carcinomas. There is also evidence that environmental exposure related with cancer formation (Heather, et al. J. Cell. Biochem. 25S:15-22, 1996, Abstract). Heather et al. teach that polymorphisms in genes controlling aromatic amine metabolism provide at least a partial explanation for ethnic and individual susceptibility to bladder cancer. Similar studies have examined genetic polymorphisms in the metabolism of tobacco smoke and lung cancer risk, red meat and colorectal cancer, and aflatoxin and liver cancer (Heather, Abstract, sec. parag). Similarly, Brandau et al. (Eur. Urol. 39:491-497, 2001) teach that [t]he transformation of a normal into a malignant cell is a multistep mechanism, which involves various alterations on the molecular and genetic level. As in most other malignancies the generation of bladder cancer is caused by the

accumulation of various molecular changes. The expression of oncogenes (ras, erbB-2 and EGF receptor), tumor-suppressor genes (Rb, p53), cell-cycle genes (p15, p16) and DNA-repair genes is altered mostly by mutation or chromosomal aberration (Brandau, Abstract). Taken together, art teaches that the development of cancer has multicauses and multisteps. The specification only state RB and E2F for hyperproliferation disease including cancer treatment. Further, at the time of filing, Chellappan (Mol. Cell. Differ. 2:201-220, 1994) teaches that E2F exists in complexes with different cellular proteins such as the retinoblastoma tumor suppressor protein, p107, p130, cyclins A and E, and kinase ckd2. E2F is emerging as a key player in cell cycle regulation, differentiation, and apoptosis. (Chellappan, Abstract). Arroyo et al. (Mol. Cell. Biol. 13:6537-6546, 1993) teach that the E2F-pRB complex correlates with a stimulation of the E2F-dependent trascription. In the S phase of the cell cycle, E2F forms a complex with p107, cyclin A, and the cdk2 kinase (E2F-cyclin A complex) (Arroyo, Abstract). Dyson (J. Cell Sci. Suppl. 18:81-87, 1994) teaches that the interaction of pRB and E2F leads to the inhibition of E2F-mediated transactivation. Most of the genes that are known to be controlled by E2F have key roles in the regulation of cell proliferation (Dyson, Abstract). Brechot (Curr. Opin. Genet. Devel. 3:11-8, 1993) teaches that cyclin A is involved at two major check-points (G1-S and G2-M) of the cell cycle. The modification of cyclin A expression in a human liver cancer by the insertion of hepatitis BV viral DNA into the cyclin A gene, and binding of cyclin A to the oncogenic E1A viral protein in

adenovirus-infected cells suggest that the cyclin is implicated in human carcinogenesis. In addition, cyclin A might also be considered as a marker for tumor-cell proliferation in oncology (Brechot, Abstract). Although the specification states to use a RB-E2F fusion construct for treating hyperliferative disease and states to use E2F polypeptide comprises at least the DNA binding domain, and may optionally include the cyclin A binding domain, the heterodimerization domain, and/or the transcactivatrion domain. Preferably, the cyclin A binding domain is not functional (specification, page 6, line 29 to page 7, line 6) and wild-type pRB110 or truncated version of RB, RB56 (379-928 of pRB110, specification, page 7, line 17-20) or amino acid variants of RB at positions 2, 608, 612, 788, 807, or/and 881 (specification, page 7, line21-23). There is no teaching or guidance as for a specific hyperproliferative disease which E2F domain should be used for Rb-E2F fusion polypeptide construct. No teaching or guidance as to which type of hyperproliferative disease, a construct can contain functional cyclin A (pertaining to instant claims 16-18, 20-30), to which type of hyperproliferative disease, a construct should not contain functional cyclin A (pertaining to instant claim 19), no teaching as to which type of hyperliferative disease, a RB fragment of amino acid residues of 379-928 (pertaining to instant claim 20, 22 and 26) or a RB containing substitution of amino acid residues at position 2, 608, 612, 788, 807 and/or 811 (pertaining to instant claims 23) should be used, or a fragment of E2F containing amino acid residues 95 - 286 (pertaining to instant claim 24) or 95 - 194 (pertaining to instant

claims 25 and 26) should be used. Although, the specification demonstrated cell cycle arrest and growth suppression of 5637 bladder cells by RB and RB-E2F fusion proteins (specification page 23-24, Table 1-2), this is not correlated with in vivo transgene therapy. Again, the specification also demonstrates a tissue-specific expression of E2F-RB fusions using smooth muscle alpha actin promoter (specification, page 25, Example II, and Figure 13-15 and description on page 28, line 4-30), that is still only *in vitro* cell line expression, not correlated with *in vivo* transgene expression, nor a method of treatment for a hyperproliferative disease. The only example that is related with disease model is the inhibition of restenosis using model rats with balloon injury (specification, page 29, line 15-28), the virus infection at this model experiment is allowed to have 20 minute incubation time at a high virus concentration (specification, page 29, line 29-36). And this data is only inhibition or prevention of restenosis, not a treatment of restenosis, nor correlated with any treatment of any cancer including bladder cancer. At the time of filing, Reznikoff et al. (Semin Oncol., 23:571-584, 1996) teaches that p53 and pRb alterations are also known to occur in early stage bladder carcinoma (Reznikoff, Abstract). Carducci et al. (Cancer Treat. Res., 88:219-34, 1996) teach that [c]ancer pathogenesis has a genetic basis, and the disease is clearly the product of the interaction of epigenetic factors and genetic alterations, where a series of genetic abnormalities accumulate in a cell, resulting in neoplasia. Corrective gene therapy is directed at preventing or reversing steps in the pathophysiology of the disease by

insertion of a gene into disease tissue, which corrects a critical pathway in neoplasia (Carducci, page 225, third full parag. line 1-6), corrective gene therapy requires ultimately that 100% of cancer cells be corrected, or inevitably malignant clones can expand and metastasize (Carducci, page 226, third parag. line 2-4), and correcting one genetic defect in a multistep process of genetic hits may not be sufficient once the cancer has produced a fully invasive and metastatic clone (Carducci, page 226, third parag. line 6-8). Taken together, Reznikoff et al. and Carducci et al. teach to correct one genetic defect in a multistep process of cancer may not sufficient for cancer treatment especially when cancer has produced a fully invasive clone to correct the defect in an earlier step such as to correct pRB alteration in bladder cancer may not be sufficient. Further more, the specification does not provide teaching or guidance as how to reach a virus infection condition that is correlated with the condition showed in the example of inhibition of restenosis as to have 20 minute incubation of virus vector with a targeting cell for *in vivo* gene therapy so that a similar result can be expected. Although the applicant claims a method for treatment of a hyperproliferative disorder in a patient by administering to a patient a therapeutically effective dose of a fusion polypeptide (pertaining to instant claims 16, 18-30), or a nucleic acid that encoding the fusion polypeptide (pertaining to instant claim 17), there is no teaching or guidance in the specification as which specific vector should be used for delivery DNA or polypeptide to any specific targeting cells for any specific disorder. There is only general description such as

that the constructs of the instant invention can be introduced into the tissue of interest *in vivo* or *ex vivo* by a variety of methods (specification, page 14, line 7-9), a list of reference regarding using virus vectors (specification, page 14, line 16-26), or liposomes (specification, page 17, line 31 to page 18, line 8) for a construct delivery. But no guidance as how to targeting specific cells by selecting different vectors for transgene delivery for each specific disorder encompassed by the claims.

The unpredictability result in gene therapy has been widely recognized in the arts since the time of filing (Carducci et al., Cancer Treat. Res. 88:219-234, 1996; Anderson, Nature 392:25-30, 1998; Nishikawa et al., Human Gene therapy 12:867-870, 2001, Rozenberg et al., S.T.P. Pharma Sciences 11:21-30, 2001; and Balicki, Medicine 81:69-86, 2002). Carducci et al. (1996) teach that Gene therapy as clinical research is still in its earliest stages (Carducci, Abstract) and [w]ithout gene transfer vectors that are efficient in transferring the therapeutic information, there cannot be a clinically meaningful gene therapy (Carducci, page 221, sec. full parag. line 1-2). Anderson (1998) teaches that the challenge of developing gene therapy as an efficient and safe drug-delivery system is more difficult to achieve than many investigators had predicted. The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome (Anderson, page 25, left col. sec. parag.). Rozenberg et al. (2001) teach that the choice of gene delivery vector is a key factor for the success of gene therapy application. It determines the efficiency

of the gene packaging, unpackaging, expression and delivery to the site of interest (Rozenberg, Abstract). Balicki (2002) compares several vectors, such as Retrovirus, Adenovirus, Lentivirus, Adno-Associated Virus, Herpes Simplex Virus in different generation as well as liposome, protein/peptide and naked DNA, by means of cell target, chromosomal integration and immunogenicity (Balicki, page 70, Table 1) and teaches that the most common and useful strategy is to deliver the gene of interest to the nucleus and points out the extracellular barriers for such delivery include degradative enzymes (Balicki, page 70, left col. first parag.). Further, Nishikawa et al (2001) teach that development of an efficient method for introducing a therapeutic gene into target cells *in vivo* is the key issue in treating genetic and acquired diseases by gene therapy (Nishikawa, Abstract). Nishikawa et al. further teach that the physicochemical properties of a DNA-vector complex will affect its passage through capillaried, extravasation, capture by the mononuclear phagocytes, and uptake by target cells (Nishikawa, page 862, col. 1 first full parag.). Taken together, the art teaches that gene delivery is specific by each vector and each encoded transgene for each cell garget. Thus, the specification fails to provide any guidance regarding to use any specific vector with the construct elected for any specific hyperproliferative disease as encompassed by the claims. It is noted that case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out, how to use it, for themselves (see In re Gardner et al. 166 USPQ 138 (CCPA 1970). The

specification only teaches what is intended to be done, but does not actually teach how to do that which is intended.

As the specification fails to provide any evidence or guidance to teach the skilled artisan how to use wild type RB or RB56 or its variants with point mutation at specified residues (specification, page 7, line 21-23) in combination with any E2F with or without cyclin A binding domain to form a construct for any specific hyperproliferative disorder, fails to provide guidance regarding vector selection for each specific targeting cell transgene delivery for each specific disorder, fails to provide any evidence as any hyperproliferative disorder can be cured by applying any RB-E2F construct, the claimed methods are not enabled. Due to the lack of direction and guidance, multiple causes and multiple steps involved in cancer formation, unpredictable gene delivery in gene therapy as the result of the viral vector used and the gene encoded, no direction or guidance as how to combine each claimed RB variants with each E2F variant for each specific hyperproliferative disorder, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 34-36, as written do not provide further limitation to claim 16 because a different product is actually administered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Liping Chen, Ph.D.
Patent Examiner
Group 1632

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